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The influence of solvent molecules on NMR spectrum of barbituric acid in the DMSO solution

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Abstract: This work shows the modification of barbituric acid (BA) chemical shifts by dimethylsulphoxide (DMSO) molecules. The discussed changes are caused by creation of the H-bonded associates formed by barbituric acid with DMSO in solution. Free molecule of barbituric acid, the cluster of BA with two DMSO molecules and two different clusters of BA with four DMSO units are taken into consideration. The chemical shifts of these systems have been calculated and the obtained results have been compared with experimental data. Theoretical calculations predict a significant downfield shift for imino protons of barbituric acid involved in intermolecular -N-H...DMSO hydrogen bonds. The influence of the solvent molecules on other nuclei chemical shifts, especially protons of barbituric acid methylene group, is also reported.

The calculations have involved Hartree-Fock and several Density Functional Theory methods. All methods correctly describe experimental ^{1}H and ^{13}C NMR spectra of barbituric acid. The best consistence between experiment and theory is observed for the BLYP functional. Four approximations of magnetic properties calculations embedded in the Gaussian'98 package have been tested. The results of the performed calculations indicate that from a practical point of view the GIAO method should be preferred.

Keywords: Barbituric acid, NMR spectroscopy, chemical shifts, theoretical calculations

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1 Introduction

Nuclear Magnetic Resonance (NMR) is the leading method in organic compounds studies. As other spectroscopies, NMR cannot be used without proper methods of experimental data interpretation. Selected experimental rules are applied to assign NMR spectra signals to the nuclei in molecules [1]. Theoretical methods are very helpful in the interpretation of Nuclear Magnetic Resonance spectra [2].

In most cases, for the theoretical explanation of the NMR spectrum, gas-phase calculations are performed. On the other hand, experimental data are usually collected in solutions. It is obvious that solute and solvent molecules must interact during the solution process. Such interactions can strongly influence the experimental NMR spectra [3]. Therefore, obtained for isolated molecules, theoretical chemical shifts are not always in agreement with the experimental data.

Dimethylsulphoxide (DMSO) is one of the most common solvents used in the Nuclear Magnetic Resonance spectroscopy. It is an aprotic and polar solvent. Its oxygen atoms are very often involved in strong hydrogen bonding interactions with the acidic protons of solute molecules (usually protons of -OH, -NH or -SH moieties). In such a bonding, DMSO withdraws the electron density from the hydrogen atoms involved, and therefore, these protons signals are shifted downfield [4, 5].

In this work we study the influence of the solvent (deuterated DMSO) on chemical shifts changes of the hydrogen bonded solute molecule. Barbituric acid (BA) has been selected as a model compound. This molecule is rather small and symmetric. Because of that, its NMR spectra are not very complicated and the signals can be easily assigned to the nuclei. In heavy water solution, all barbituric acid protons are replaced by deuterons [6]. This property demonstrates that all barbituric acid protons, not only protons of the imino group, are acidic and can interact with solvent molecules. Because of these, barbituric acid is a valuable example for studying the changes in NMR spectra upon solute-solvent interactions.

2 Experimental and computational details

In order to obtain 1D NMR spectra of mono barbituric acid molecules in DMSO solution, 40 mg of BA were dissolved in 0.7 cm^3 of deuterated DMSO (99.8 % purity, Deutero GmbH); and the NMR data were collected using the Varian Mercury - VX 300 MHz spectrophotometer operating at a proton frequency of 300.081 MHz, using a standard Varian pulse sequence with 45 degrees excitation pulses. ^{1}H NMR spectra were acquired with 16 scans, 4200 Hz spectral width, 1 s relaxation decay. Data were zerofilled up to 32k, apodized with 0.1 Hz exponential line broadening function and fourier transformed. ^{13}C spectra were recorded with WALTZ-16 modulated 1H broadband decoupling, 16000 repetitions, 18200 Hz spectral width, 1 s relaxation delay. For data processing zerofilling up to 64 k and 0.5 Hz, exponential line broadening apodization were used. Again the fourier transformation of collected data was executed. All measurements were performed

at ambient temperature. Chemical shifts for all spectra where referenced against solvent lock signal. In order to check if barbituric acid creates its aggregates (dimmers, trimers...)in this condition, the concentration of the barbituric acid was decreased by adding more deuterated DMSO to the solution (in the ratio 1:1) and recollecting NMR spectra. The whole procedure was repeated four times. All spectra obtained were the same within the error limit. Measured chemical shifts of a single barbituric acid carbon and hydrogen nuclei in deuterated DMSO were used for further interpretation.

The Gaussian'98 package [7] was used for all computations. Equilibrium geometries and magnetic properties of barbituric acid and its associates with two and four DMSO molecules were calculated at the Hartree-Fock (HF) and Density Functional Theory (DFT) levels. Within DFT approximation, several methods were employed. We used the SVWN and BLYP functionals. The first is a local density approximation (LDA) functional which consisted of an exchange part proposed by Slater [8] combined with the correlation function of Vosko et al. [9]. The latter is one of the gradient corrected functionals built from Becke's [10] and Lee-Yang-Parr's [11] parts. The B3LYP [12] method was also applied. It belongs to the adiabatic connection methods (ACM) which combine Hartree-Fock and DFT procedures. The basis set influence on the obtained results correctness was also investigated. That is why three basis sets, namely 6-311G (lowest basis set), 6-311++G(d,p) (middle basis set) and 6-311++G(3df,2pd) (highest basis set), were used for calculations.

The usefulness and correctness of the four theoretical methods available in the Gaussian package, namely, SGO [13], IGAIM [14], CSGT [15] and GIAO [16] were tested. Theoretical chemical shifts were calculated in respect to tetramethylsilane (TMS). All calculated structures were visualized using the Molden [17] program.

3 Results and discussion

Several tautomers of barbituric acid can be considered. It has been shown [18, 19] that barbituric acid exists as the tautomer consisted of three keto, two imino and one methylene groups, see Fig. 1. This structure has been used for calculations.

General assignment of signals in the ^{1}H and ^{13}C NMR spectra is provided in Tables 1 and 2. The experimental data have been compared with the results of theoretical calculations. Among all theoretical methods tested, the SGO approximations yielded the worst results that are not presented. IGAIM and CSGT methods have predicted exactly the same (relative to TMS) theoretical chemical shifts. Therefore, these methods are presented jointly as CSGT / IGAIM. Within the basis sets employed, only 6-311++G(d,p) and 6-311++G(3df,2pd) have provided theoretical data of value.

Three signals are expected and observed in the ^{13}C NMR spectrum of barbituric acid. An interpretation of this spectrum is not difficult. Signals at 151.51 ppm and 39.27 ppm are assigned to C_1 and C_7 nuclei, respectively (for atom numbering scheme see Fig. 1). The third signal (168.48 ppm) is common (due to molecular symmetry of barbituric acid) for C_5 and C_6 nuclei. Differences between theory and the experiment are not significant.

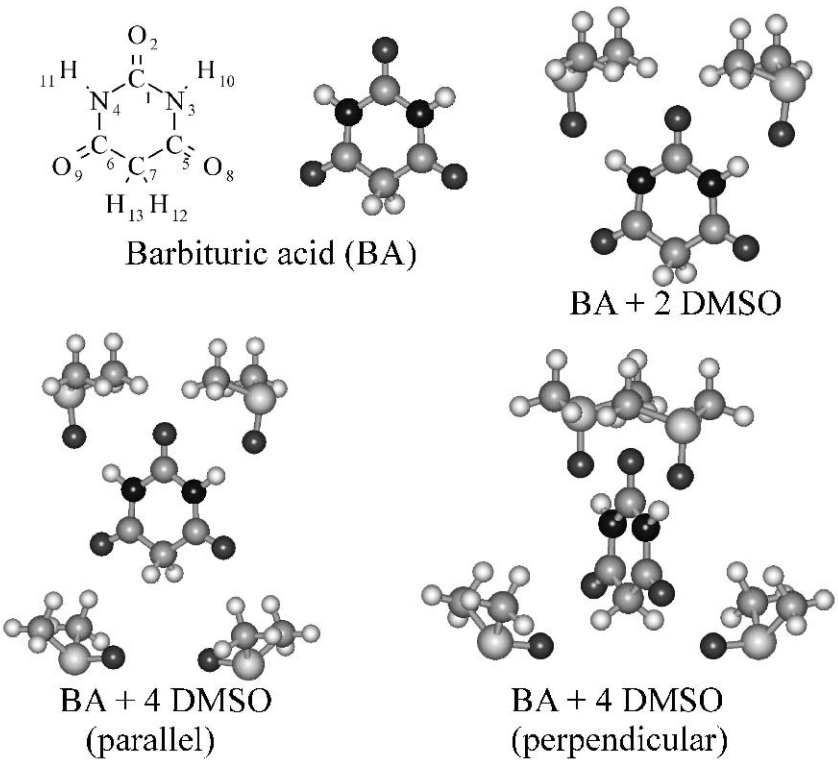

Fig. 1 Atom numbering scheme and molecular structures of the barbituric acid and its associates with DMSO molecules studied in this work.

Considering GIAO calculations involving only the single BA molecule, the B3LYP method provides the most accurate results. Contrary, the SVWN approximation gives the poorest ones. This statement is true for both basis sets presented [6-311++G(d,p) – Table 1 and 6-311++G(3df,2pd) - Table 2]. Basis set improving [to the 6-311++G(3df,2pd) one] does not vary the results significantly. The results obtained for the highest basis set used are approximately 1 ppm closer to the experimental data than those in the middle basis set [6-311++G(d,p)] for all methods employed. Regarding the CSGT / IGAIM calculations derived from the middle basis set, results (except for the HF method) seem to be a bit worse than corresponding GIAO data. They improve in the high basis set.

The ^{1}H NMR spectrum is even more simplified and possesses only two signals. One of them (at 3.47 ppm) originates from the protons of the methylene group. The origin of the second must be connected with the protons of the -NH groups. In this case, a significant disagreement is observed between theory and the experiment. For the isolated barbituric acid molecule, theoretical methods predict the chemical shifts of these protons ranging from 6.41 to 6.61 ppm [6-311++G(d,p) basis set, GIAO method]. The experimental value appears at 11.1 ppm, see Table 1. Theoretical values of imino protons predicted for the extended 6-311++G(3df,2pd) basis set seem to be slightly better, but still far from the experimental data. Why such an enormous discrepancy (ca. 4.5 ppm)? We believe that it is generated by intermolecular interactions of the barbituric acid with the solvent, in

Table 1 Theoretical GIAO and CSGT (in parentheses) chemical shifts of barbituric acid and its complexes in the 6-311++G(d,p) basis set.

Nucleus	HF	SVWN	BLYP	B3LYP	Experiment
			BA		
$\mathbf{C_1}$	148.05 (151.02)	145.29 (143.58)	146.35 (139.74)	147.79 (144.74)	151.51
$\mathbf{C_5}$, $\mathbf{C_6}$	164.27 (168.09)	162.48 (161.33)	163.43 (156.67)	164.84 (161.81)	168.48
$\mathbf{C_7}$	32.21 (30.06)	34.80 (32.62)	37.28 (30.96)	36.07 (32.35)	39.27
$\mathbf{H_{10}}$, $\mathbf{H_{11}}$	6.41 (6.03)	6.61 (5.36)	6.56 (5.25)	6.59 (5.60)	11.10
$\mathbf{H_{12}}$, $\mathbf{H_{13}}$	2.93 (2.29)	3.15 (1.90)	3.05 (1.84)	3.04 (2.07)	3.47
			BA + 2DMSO		
$\mathbf{C_1}$	156.81 (154.33)	158.31 (156.43)	155.55 (153.36)	157.86 (155.48)	151.51
$\mathbf{C_5}$, $\mathbf{C_6}$	165.64 (162.72)	165.97 (163.67)	165.31 (162.52)	166.68 (163.98)	168.48
C7	32.97 (28.83)	36.78 (33.32)	38.59 (35.25)	37.26 (33.75)	39.27
$\mathbf{H_{10}}$, $\mathbf{H_{11}}$	10.89 (8.39)	15.12 (12.83)	11.74 (9.48)	12.06 (9.71)	11.10
$\mathbf{H_{12}}$, $\mathbf{H_{13}}$	2.83 (1.73)	3.04 (2.11)	2.96 (2.01)	2.95 (1.96)	3.47
			BA + 4 DMSO (parallel)		
$\mathbf{C_1}$	157.04 (154.50)	158.38 (156.14)	156.28 (153.45)	158.07 (155.55)	151.51
$\mathbf{C_5}$, $\mathbf{C_6}$	168.86 (166.34)	170.87 (168.83)	167.14 (164.76)	169.75 (167.42)	168.48
$\mathbf{C_7}$	32.96 (29.38)	43.28 (39.44)	38.53 (35.56)	37.55 (34.64)	39.27
$\mathbf{H_{10}}$, $\mathbf{H_{11}}$	10.73 (8.43)	14.90 (12.77)	11.89 (9.76)	12.03 (9.83)	11.10
$\mathbf{H_{12}}$, $\mathbf{H_{13}}$	3.61 (2.62)	5.96 (4.44)	3.36 (2.66)	3.72 (2.87)	3.47
			BA + 4 DMSO (perpendicular)		
$\mathbf{C_1}$	159.76 (157.43)	158.23 (157.43)	157.34 (154.52)	159.10 (156.78)	151.51
$\mathbf{C_5}$, $\mathbf{C_6}$	170.75 (167.69)	170.78 (168.97)	168.80 (165.87)	170.40 (167.47)	168.48
$\mathbf{C_7}$	36.03 (31.53)	49.75 (45.94)	41.02 (36.80)	39.40 (35.20)	39.27
$\mathbf{H_{10}}$, $\mathbf{H_{11}}$	9.86 (7.76)	15.01 (13.23)	10.93 (8.92)	11.22 (9.10)	11.10
$\mathbf{H_{12}}$, $\mathbf{H_{13}}$	2.70 (1.61)	7.23 (5.50)	4.89 (3.20)	5.07 (3.25)	3.47

this case, the DMSO molecules. Thus far, the theoretical chemical shift of the isolated barbituric acid molecule has been taken into account. But this molecule can interact with the solvent. In order to check this hypothesis, the clusters of barbituric acid with DMSO molecules should be taken into account. The crucial importance of the hydrogen bonds formation in intermolecular interactions should be noted. The engagement of a acidic proton in a strong hydrogen bond (-N-H...O= system in our case) results in their downfield shifting in ^{1}H NMR spectra. A dependence, such as this one, has been found earlier for protons involved in the hydrogen bonded carboxylic [20] and salicylohydroxamic [21] acids aggregates.

A complex consisting of two DMSO molecules (BA*2DMSO) connected with the barbituric acid molecule by -N-H...O= hydrogen bonds has been built and used for

Table 2 Theoretical GIAO and CSGT (in parentheses) chemical shifts of barbituric acid and its complexes in the 6-311++G(3f,2pd) basis set.

Nucleus	HF	SVWN	BLYP	B3LYP	Experiment
			BA		
$\mathbf{C}_1$	149.33 (150.01)	146.11 (146.90)	147.10 (147.79)	148.70 (149.43)	151.51
$\mathbf{C}_5$, $\mathbf{C}_6$	165.46 (165.89)	164.10 (164.60)	164.36 (164.78)	165.87 (166.33)	168.48
$\mathbf{C}_7$	32.24 (32.34)	34.72 (35.22)	37.27 (37.58)	36.03 (36.31)	39.27
$\mathbf{H}_{10}$, $\mathbf{H}_{11}$	6.63 (6.63)	6.94 (6.93)	6.84 (6.82)	6.86 (6.85)	11.1
$\mathbf{H}_{12}$, $\mathbf{H}_{13}$	2.97 (2.99)	3.19 (3.22)	3.09 (3.11)	3.08 (3.11)	3.47
			BA + 2DMSO		
$\mathbf{C}_1$	157.87 (158.40)	158.19 (159.51)	146.86 (147.71)	158.40 (159.10)	151.51
$\mathbf{C}_5$, $\mathbf{C}_6$	166.55 (166.94)	167.08 (167.45)	156.74 (157.22)	167.57 (167.92)	168.48
$\mathbf{C}_7$	32.86 (32.88)	36.14 (36.75)	33.45 (33.76)	36.95 (37.19)	39.27
$\mathbf{H}_{10}$, $\mathbf{H}_{11}$	10.73 (10.73)	15.52 (15.54)	10.11 (10.11)	12.12 (12.10)	11.1
$\mathbf{H}_{12}$, $\mathbf{H}_{13}$	2.78 (2.80)	3.01 (3.03)	2.30 (2.32)	2.91 (2.93)	3.47
			BA + 4 DMSO (parallel)		
$\mathbf{C}_1$	157.83 (158.27)	156.03 (158.59)	155.52 (156.85)	157.66 (158.83)	151.51
$\mathbf{C}_5$, $\mathbf{C}_6$	169.50 (169.92)	170.94 (171.59)	167.74 (168.17)	170.14 (170.66)	168.48
$\mathbf{C}_7$	32.99 (32.93)	42.14 (42.63)	38.24 (38.76)	36.91 (37.60)	39.27
$\mathbf{H}_{10}$, $\mathbf{H}_{11}$	10.58 (10.58)	15.21 (15.25)	11.96 (11.95)	12.05 (12.04)	11.1
$\mathbf{H}_{12}$, $\mathbf{H}_{13}$	3.31 (3.32)	5.19 (5.23)	3.30 (3.32)	3.47 (3.46)	3.47
			BA + 4 DMSO (perpendicular)		
$\mathbf{C}_1$	160.26 (160.94)	159.64 (160.01)	156.71 (157.96)	159.32 (160.17)	151.51
$\mathbf{C}_5$, $\mathbf{C}_6$	170.82 (171.36)	171.82 (172.48)	168.98 (169.53)	170.69 (171.18)	168.48
$\mathbf{C}_7$	35.48 (35.58)	49.20 (49.85)	40.26 (40.33)	38.68 (38.77)	39.27
$\mathbf{H}_{10}$, $\mathbf{H}_{11}$	9.52 (9.53)	15.22 (15.26)	11.00 (11.00)	11.26 (11.25)	11.1
$\mathbf{H}_{12}$, $\mathbf{H}_{13}$	2.60 (2.60)	7.11 (7.09)	4.51 (4.57)	4.64 (4.69)	3.47

calculations, see Fig. 1. Theoretical chemical shifts of the BA*2DMSO supermolecule are also collected in Tables 1 and 2. After the solvent molecules have been introduced, the calculated (by the GIAO method) chemical shifts of the NH groups protons are significantly shifted downfield and the theoretical data matches the experiemental value of 11.1 ppm better. They are comparable for all methods (calculated values vary from 10.89 to 12.06 ppm for the 6-311++G(d,p) basis set) except SVWN. In the latter case, the calculated chemical shift is significantly higher (15.12 ppm) than that obtained by other theoretical calculations and the experimental value.

On the other hand, the CSGT / IGAIM method in the middle basis set provides poorer results. Again the SVWN approximation predicts the largest chemical shift of imino protons (12.83 ppm). The values calculated using the Hartree-Fock method and

other DFT functionals vary from 8.39 to 9.71 ppm.

The GIAO results recalculated in the highest basis set used in calculations do not differ significantly from the 6-311++G(d,p) ones. For example, B3LYP predicts 12.12 and 12.06, whereas BLYP predicts 10.11 and 11.74 in the middle and high basis sets, respectively. However, results obtained by the CSGT / IGAIM method are significantly better when the high 6-311++G(3df,2pd) basis set is used. It should be noted that calculations performed in the 6-311++G(3df,2pd) basis set give essentially the same values for the GIAO and CSGT / IGAIM calculations.

In conclusion, it is obvious that the GIAO method is more convenient than the CSGT / IGAIM method. The latter works properly mostly in very high basis sets whereas GIAO gives satisfactory results also in the middle basis sets.

The values of carbon nuclei are usually closer to the experiment in BA*2DMSO associates than in the single molecule calculations. The data in Tables 1 and 2 show that when the solvent molecules are present, the BLYP approximation gives the most accurate theoretical description of barbituric acid NMR spectra.

The presentation above demonstrates that the introduction of two DMSO molecules bonded to the imino group protons significantly improves the consistence of theoretical and experimental data. The improvement is promising for the N-H protons and is also perceptible for the carbon nuclei. Nevertheless, the thorough analysis of the BA and BA*2DMSO theoretical data reveals that there is something unclear (unfamiliar behavior) regarding the protons of the barbituric acid methylene group. The experimental chemical shift of these protons is 3.47 ppm. The mean calculated values at the HF/6-311++G(d,p) level (results of all quantum methods included) obtained for a single molecule are 3.08 and 3.11 for GIAO and CSGT / IGAIM, respectively. The corresponding mean values estimated for the complex are equal to 2.75 and 2.77 ppm. The results for the BA aggregate with two dimethylsulphoxide molecules are lower (by about 0.35 ppm) what makes the match with experimental values even worse. Although this difference may not seem significant, it is about 10 % of the discussed protons experimental chemical shift.

We postulate that the imbalance in the solvent interactions of the imino and methylene groups is the reason of the observed data deterioration. In the BA*2DMSO supermolecule, one part of the complex (imino groups) can interact with the solvent molecules whereas the analogical interaction for another part (methylene group) is prohibited. As it was mentioned earlier, the protons of the barbituric acid methylene group are quite acidic and their interactions with polar solvents should not be neglected.

We have decided to add two more DMSO to our BA*2DMSO complex. These additional molecules are placed in close proximity to the methylene group area. At least two conformations of the new DMSO molecules are possible. The first possible conformation places them parallel to the barbituric ring plane, the second one places them in a perpendicular manner (Fig. 1).

The experiment-theory gap of the methylene protons is much less for the parallel conformation of the two additional DMSO units. This is true for all the methods and basis sets involved in the presented calculations. Contrary, the quality of the other nuclei

results is more or less the same as for the BA*2DMSO complex. It seems that a parallel positioning of the third and fourth DMSO units is much more probable.

We conclude that the theoretical model of the associate consisting of BA and four DMSO molecules (two DMSO connected through hydrogen bonds to the barbituric acid N-H groups and next two close to the methylene group in the parallel manner to the barbituric ring) is complete and describes all experimental features of barbituric acid NMR spectra in a qualitative manner.

4 Conclusions

On the basis of the performed calculations the following conclusions can be made. First, the solvent effects can play the crucial role in the theoretical NMR spectra interpretation. The inclusion of the solvent molecules is important when solvent and solute units create intermolecular complexes through hydrogen bonds. The electron density around protons involved in a hydrogen bond decreases, and these proton' chemical shifts move toward a weaker magnetic field. Theoretical methods neglect this effect in case of single molecule calculations. Therefore, the discrepancy between theoretical results for an isolated molecule and experimental data is very significant. For molecules more complicated than the one studied in this work (barbituric acid) this effect can be the reason for the misinterpretation of nuclear magnetic resonance spectra.

It has been shown that for the barbituric acid, the solvent effect is important not only for the protons of the imino moieties but also for the protons of the methylene group. On the other hand, the introduction of the solvent molecules improves also the theoretical data correctness for carbon nuclei.

The best results for the isolated molecule have been obtained using the B3LYP functional. For calculations of the NMR properties of barbituric acid - dimethylsulphoxide complexes, the BLYP functional provides data that are closest to the experiment. The SVWN functional has given the poorest results in both, single molecule and solute-solvent associates calculations. The usefulness of the Hartree-Fock method is acceptable.

Last, if anybody chooses to interpret NMR spectra using the Gaussian package, GIAO or CSGT / IGAIM methods (according to the obtained results CSGT and IGAIM methods are equivalent) are available. The first method works properly in middle basis sets, whereas the latter requires very high ones. Because of that property, the GIAO method should be preferred in order to save computer time. It is not advisable to study NMR properties using the SGO method because its results are very inaccurate.

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